

REMARKS**Amendments**

Claims 5-7, 16, 17, 19 and 20 have been canceled, claims 1-4, 11-15, 22 and 24-35 have been withdrawn, claims 8-10, 18, 21 and 23 have been amended, and claims 36-39 are added. Upon entry of the amendment, claims 8-10, 18, 21, 23 and 36-39 will be pending. Support for the added claims can be found in the specification as originally filed, for example, on page 7, lines 18-21, page 20, lines 14-28, the Examples, the Figures, and in the claims as originally filed. Accordingly, no new matter is introduced.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Objections

Claims 10, 17, 18 and 20 are objected to for improper dependency. The claims have been amended accordingly.

Claim 19 is objected to on the ground that a pseudopregnant mouse gives birth. Contrary to the Examiner's assertion, as shown in the literature (for example, Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)(p. 542, Figure 8-70)(copy of relevant page attached)), the pseudopregnant female gives "birth" to the chimeric mouse. The terminology would be clearly understood by one skilled in the art.

Withdrawal of the objection is respectfully requested.

Rejections***Rejections under 35 U.S.C. § 101/112 1st paragraph***

The Examiner has rejected claims 5-10, 16-21 and 23 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility for the reasons of record.

1. *The Utility Requirement*

According to 35 U.S.C. § 101, “[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . .”

Under the Patent Office’s Utility Requirement Guidelines:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

...

If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard.

The standard for “credible” is defined as:

... whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office’s own guidance to Examiners:

Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.

Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., “question”) the truth of the statement of utility. . . . To do this,

Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered “false” by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts.

Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler’s arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art “would immediately appreciate why” knockout mice are useful. As a general principle,

knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.

...

In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(<http://www.genome.gov/pfv.cfm?pageid=10005834>)(emphasis added)(copy attached).

Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (*Mus musculus*) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic

mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.

...

A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

Null-reporter alleles should be created

The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as

“research tool,” “intermediate” or “for research purposes” are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.

(p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous “knockout”, which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.

(preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.

(p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.

Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

2. *The Claimed Subject Matter Has Utility in View of at Least One Commercial Sale as Described in the Enclosed Declaration of Robert Driscoll.*

Commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, at least one (1) large pharmaceutical company has ordered the presently claimed mouse. This acceptance more than satisfies the practical utility requirement of section 101 as it cannot be reasonably argued that a claimed invention which is actually being used by those skilled in the art has no "real world" use. (see, for example, *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success); (Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand."))

The Examiner notes that Applicant has failed to provide evidence of commercial use. As evidence of such sales and purpose of such use, attached hereto is a Rule 132 Declaration from Robert Driscoll, Vice President of Intellectual Property & Legal Affairs of Assignee, Deltagen.

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

3. *The Claimed Subject Matter is Useful for a Particular Purpose*

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice. Utility of the claimed knockout mouse would be apparent to, and considered credible by, one of skill in the art, as the role of knockout mice in studying any of these conditions is both specific and substantial.

The Examiner argues that claimed subject matter lacks utility because the use of the claimed mouse to screen for drugs to treat an unknown disease is not specific (page 11). The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proffered by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented

actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, citing *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated specific phenotypes. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated.

Definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to satisfying the utility requirement. It is enough that the claimed mouse demonstrates phenotypes, relative to a wild type control mouse, and that knockout mice are recognized in the art as models for determining gene function, both in mice and in humans. According to Austin et al.:

Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.

(p. 921)(emphasis added).

In addition, as pointed out by Doetschman, one clearly skilled in the art, (*Laboratory Animal Science* 49:137-143, 137 (1999)(copy attached), the phenotypes observed in mice do correlate to gene function:

The conclusions will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function, that we should let the unexpected phenotypes lead us to the specific cell, tissue, organ culture, and whole animal experiments that are relevant to the function of the genes in question, and that the absence of phenotype indicates that we have not discovered where or how to look for a phenotype.

(emphasis added).

In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be

without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

The observations and conclusions recited in the specification were made by those skilled in the art. Applicant points out that all of the employees and consultants involved in Deltagen's pathology group are either MD's or DVM's, and many in addition hold PhD degrees. At least sixteen (16) of the employees or consultants are board certified ACVP or ABP. Unless the Examiner has reason to doubt the credibility of the reported results, the burden remains on the Examiner to set forth a *prima facie* case of lack of utility.

According to the MPEP:

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;

Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). Thus, the cited portions of the MPEP guidelines relate to the situation where further research is required to establish or confirm any utility. Such is not the case here. Knockout mice have a well-known use in the study of gene function. In the present

case, the present invention does not require further research to establish a utility. Applicant has determined that the secreted protein gene is associated with, for example, depression. The Applicant has provided an immediate benefit to the public – as demonstrated by the transfer of the claimed invention to at least one large pharmaceutical company. Whether additional research is required to identify drugs capable of targeting the secreted protein gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

The Examiner questions how a mouse that is less depressed can be used to screen for drugs.

First, as pointed out above, the presently claimed mouse has been delivered to at least one large pharmaceutical company. Clearly, those skilled in the art know how to use the claimed invention.

Second, according to the specification:

When tested in the tail suspension test, homozygous mutant mice spent significantly less time immobile than did wild-type mice (Figure 2), indicating less of a propensity for endogenous depression as compared to controls

Rather than indicating a depressed phenotype, these results indicate that a disruption in the secreted protein gene of the present invention may cause an anti-depressive condition, similar to that seen with administration of anti-depressant drugs. These homozygous mutants spent less time immobile, indicating less of a propensity for endogenous depression as compared to controls.

(Example 3).

In one embodiment, the present invention provides a method of identifying agents having an effect on secreted protein expression or function. The method includes measuring a physiological response of the animal, for example, to the agent, and comparing the physiological response of such animal to a control animal, wherein the physiological response of the animal comprising a disruption in a secreted protein gene as compared to the control animal indicates the specificity of the agent.

(specification, p.20). Since the mouse demonstrates behavior similar to that seen with administration of anti-depressant drugs, it would be desirable to find agents which down regulate the gene or antagonize the secreted protein. The homozygous mouse can be used to determine the specificity of agents by comparing the effect of the agent on controls.

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the

gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying secreted protein gene function with respect to the cited phenotypes, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 5-10, 16-21 and 23 have been rejected for lack of enablement, as the claimed invention allegedly lacks utility. As set forth above, it the Applicant's position the claimed invention satisfies the utility requirement and therefore one skilled in the art would clearly know how to use the invention. Withdrawal of the rejections is respectfully requested.

The Examiner argues that the art at the time of filing could not predict the phenotype of a knockout mouse.

Applicant notes that claim 8 does not recite any phenotypes. The specification enables the claimed invention: a transgenic mouse having a null secreted protein allele. With regard to the dependent claims reciting phenotypes, predicting phenotypes *a priori* must be distinguished from reproducibility of the phenotype of the claimed mouse. The general rule is that disruption of the coding sequence by a positive selection marker, as taught in the specification, will result in a null allele, which by definition involves ablation of gene function (see, for example, Hasty et al., *Gene Targeting, Principles, and Practice in Mammalian Cells* in *Gene Targeting: A Practical Approach*, ed. Joyner, Oxford University Press 2000, p. 5). Ablation of function is expected to result in the same phenotypic response.

The claims have been limited to mice, addressing the Examiner's concerns.

The claims as amended define the secreted protein gene as the mouse homolog of SEQ ID NO:1, addressing the Examiner's concerns.

With regard to the recitation of phenotypes, claims have been amended to recite phenotypes observed in the homozygous mouse.

The claims have been amended to recite that the mouse comprises a genomic disruption. Applicant submits that the specification enables the claims as amended, and respectfully requests withdrawal of the rejections.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 5-10, 16-21 and 23 stand rejected for allegedly failing to meet the written description requirement. The claims have been amended to reflect that the secreted protein gene is the mouse homolog of SEQ ID NO:1.

Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

Claims 5-10, 19 and 20 stand rejected as being anticipated by Bucay, which is cited as teaching a transgenic mouse having a disrupted osteoprotegerin gene.

The claims have been amended to reflect that the secreted protein gene is the mouse homolog of SEQ ID NO:1. Bucay does not disclose such a mouse.

Withdrawal of the rejection is respectfully requested.

Claims 5-10, 19 and 20 stand rejected as being anticipated by Zhang, which is cited as teaching a transgenic mouse having a disrupted UG gene.

The claims have been amended to reflect that the secreted protein gene is the mouse homolog of SEQ ID NO:1. Zhang does not disclose such a mouse.

Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.


Respectfully submitted,

Date

5-13-85

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